Clinical Edit Criteria Proposal

Drug/Drug Class: **Emend® (Aprepitant) / Chemotherapy Anti-emetic**

Prepared for: Missouri Medicaid
Prepared by: Heritage Information Systems, Inc.

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose: The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use.

Dosage Forms & Manufacturer: 80mg, 125mg capsule and 80mg/125mg combination Pak
Merck

Summary of Findings: Aprepitant is a selective antagonist of human substance P/neurokinin receptors that has demonstrated efficacy in the treatment of chemotherapy-induced nausea and vomiting when used in combination with other antiemetic agents. It is the first agent approved for the prevention of both acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Aprepitant appears to augment the antiemetic activity of 5-HT3-receptor antagonists and the corticosteroid dexamethasone and may provide a useful combination therapy option for patients receiving highly emetogenic cancer chemotherapy.

Status Recommendation:
☐ Prior Authorization (PA) Required
☐ Open Access
☒ Clinical Edit

Type of PA Criteria:
☐ Increased Risk of ADE
☐ Non-Preferred Agent
☐ Appropriate Indications
☐ PA Not Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guiding appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Emend® is a neurokinin-1 (NK-1)-receptor antagonist (substance P antagonist). Substance P is a tachykinin (neurokinin) located in neurons of the central and peripheral nervous system where it is associated with a variety of functions, including emesis. Emend® has little or no affinity for serotonin (5-HT3), dopamine, or corticosteroid receptors. It is indicated in combination with other antiemetic agents, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Dosage Form(s)

Emend® is available in an oral capsule formulation and is supplied in strengths of 80mg and 125mg.

Manufacturer

Merck

Indication(s) [1]

Emend®, in combination with other antiemetic agents, is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

Clinical Efficacy [1-9] (mechanism of action/pharmacology, comparative efficacy)

Mechanism of action: Emend® is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK_1) receptors. It has little or no affinity for serotonin ($5\text{-}HT_3$), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CNV).

Efficacy: Several controlled clinical trials demonstrated that various regimens of oral aprepitant combined with a serotonin-3 (5-HT3)-receptor antagonist plus dexamethasone are more effective than the latter two agents or aprepitant plus dexamethasone in reducing cisplatin-induced acute and/or delayed emesis. Efficacy in these studies was primarily based upon the prevention of emetic episodes and need for rescue therapy during the acute period following cisplatin treatment (0-24 hours) and during the delayed phase (25 to 120 hours). In addition, more patients receiving an antiemetic regimen with aprepitant reported minimal or no impact of nausea and vomiting on their daily life compared to regimens without aprepitant.

	STUDY 1	STUDY 2
STUDY DESIGN	Multicenter, double-blind, parallel-group clinical trial (n=351)	Two multicenter, randomized, parallel, double-blind, controlled clinical trials (n=1,105)
INCLUSION CRITERIA	Cisplatin-naïve cancer patients aged 16 and older scheduled to receive cisplatin-based chemotherapy at a dose >=70 mg/m(2)	Patients receiving a chemotherapy regimen that included cisplatin (> 50 mg/m(2).
EXCLUSION CRITERIA	A Karnofsky score < 60; allergy or intolerance to metoclopramide, dexamethasone, or granisetron; use of another antiemetic agent within 72 hours of study day 1; an episode of vomiting or retching within 24 hours before the start of cisplatin infusion on study day 1; treatment for or history of a seizure within the past 2 years; severe concurrent illness other than neoplasia; GI obstruction or active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week before or after study day 1; hemoglobin < 8.5 g/dL, WBC < 3,500/microliter, platelets < 100,000/microliter, AST > 2 X upper limit of normal (ULN), ALT > 2 X ULN, bilirubin > 2 X ULN, alkaline phosphatase > 2 X ULN, albumin <3 g/dL, serum creatinine > 2.0 mg/dL.	Not specified
TREATMENT REGIMEN	Patients were randomized to receive granisetron (10 micrograms/kg intravenously (IV)) pre-cisplatin followed by placebo on days 2 to 5 (group 1); granisetron and aprepitant (400 mg orally (PO)) pre-cisplatin, followed by aprepitant (300 mg PO) on days 2 to 5 (group 2); aprepitant (400 mg PO) the evening before and pre-cisplatin, followed by aprepitant (300 mg PO) on days 2 to 5 (group 3); or aprepitant (400 mg PO) pre-cisplatin, followed by aprepitant (300 mg PO) on days 2 to 5 (group 4). All patients also received dexamethasone (20 mg PO) before cisplatin. Aprepitant was administered 2 hours prior to cisplatin; subsequent doses were administered every morning. Additional medication was available to treat emesis or nausea at any time.	On day 1, patients were randomized to receive aprepitant (125 mg orally (PO)) plus dexamethasone (12 mg PO) plus ondansetron (32 mg intravenously (IV)) or standard therapy with ondansetron (32 mg IV) plus dexamethasone (20 mg PO). On days 2 through 4, the aprepitant regimen group received aprepitant (80 mg PO on days 2 and 3 only) plus dexamethasone (8 mg PO daily in the AM) while the standard therapy group received dexamethasone (8 mg PO in the morning and evening).
RESULTS	In the acute period, 57%, 80%, 46%, and 43% of patients were without emesis in groups 1 to 4, respectively. In the delayed period, the proportion of patients without emesis were	**Trial 1:** A complete response (no emetic episodes and no use of rescue therapy) was observed in 73% of the aprepitant group overall

	STUDY 1	STUDY 2
	29%, 63%, 51%, and 57%, respectively.	compared to 52% overall in the standard therapy group. Complete responses during the acute and delayed phases were 89% and 75% respectively in the aprepitant group vs. 78% and 56%, respectively in the standard therapy group. **Trial 2:** A complete response was observed in 63% of the aprepitant group overall compared to 43% in the standard therapy group. Complete responses during the acute and delayed phases were 83% and 68%, respectively in the aprepitant group vs. 68% and 47% in the standard therapy group. In addition, in both studies, the estimated time to first emesis after initiation of cisplatin treatment was longer with the aprepitant regimen compared to standard therapy. Furthermore, the proportion of patients reporting minimal or no impact of nausea and vomiting on daily life was 75% vs 64%, respectively.
SAFETY	The most common adverse events were constipation, diarrhea, abdominal pain, dizziness, headache, hiccups, asthenia, and anorexia.	The aprepitant treatment regimen and standard therapy regimen were generally well tolerated.
CONCLUSION	The triple drug combination of oral aprepitant, granisetron, and dexamethasone is effective for the prevention of cisplatin-induced emesis, and more effective than granisetron and dexamethasone alone, or aprepitant and dexamethasone alone.[3]	Oral aprepitant in combination with ondansetron and dexamethasone is effective in the prevention of acute and delayed nausea and vomiting associated with highly emetogenic chemotherapy, including high-dose cisplatin, and is superior to ondansetron plus dexamethasone alone.[1]

PHARMACOKINETICS: 60% - 65% oral bioavailability; >95% protein binding; 70 L volume of distribution; extensive oxidation in the liver via CYP3A4 (major), CYP1A2 (minor), and CYP2C19 (minor) isoenzymes; 57% Urinary excretion; 45% fecal excretion; Half-life of 9 – 13 hours.

Adverse Effects [1]

MOST COMMON, > 10%	LESS COMMON, 3-10%
Asthenia/fatigue (17.8 %)	Headache (8.5 %)
Nausea (12.7 %)	Vomiting (7.5 %)
Hiccups (10.8 %)	Dizziness (6.6 %)
Constipation (10.3 %)	Dehydration (5.9 %)
Diarrhea (10.3 %)	Heartburn (5.3 %)
Anorexia (10.1 %)	Abdominal pain (4.6 %)
	Gastritis (4.2 %)
	Epigastric discomfort (4.0 %)
	Tinnitus (3.7 %)
	Neutropenia (3.1 %)
	Fever (2.9 %)
	Insomnia (2.9 %)
	Mucous membrane disorder (2.6 %)

Drug Interactions [1]

Emend® is a substrate, a moderate inhibitor, and an inducer of CYP3A4 and is also an inducer of CYP2C9. Because of this the following drugs may interact, therefore caution should be exercised when prescribing the following: warfarin, tolbutamide, phenytoin, dexamethasone, methylprednisolone, oral contraceptives, midazolam, alprazolam, triazolam, ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, nelfinavir, diltiazem, rifampin, carbamazepine and paroxetine. Emend© should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride.

Dosage and Administration [1]

DAY 1	DAY 2	DAY 3	DAY 4
Emend® 125mg orally 1 hour prior to chemotherapy	Emend® 80mg orally once daily in the morning	Emend® 80mg orally once daily in the morning	
Ondansetron 32mg IV and Dexamethasone 12mg orally 30 minutes prior to chemotherapy	Dexamethasone 8mg orally	Dexamethasone 8mg orally	Dexamethasone 8 mg orally

Cost Comparison [10] (at commonly used dosages)

Cost Per Course	$310
80mg Capsules	$100
125mg Capsules	$110

Conclusion

Aprepitant is a selective antagonist of human substance P/neurokinin receptors that has demonstrated efficacy in the treatment of chemotherapy-induced nausea and vomiting when used in combination with other antiemetic agents. It is the first agent approved for the prevention of both acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Aprepitant appears to augment the antiemetic activity of 5-HT3-receptor antagonists and the corticosteroid

dexamethasone and may provide a useful combination therapy option for patients receiving highly emetogenic cancer chemotherapy.

Approval Criteria

- diagnosis of cancer
- maximum quantity equals three tablets

Denial Criteria

- inappropriate diagnosis
- therapy exceeding 3 days

Recommendation(s)

It is recommended that clinical edits be in place for Emend®.

References

1. Emend® (aprepitant). Product labeling. Merck & Co., Inc.: Whitehouse Station, NJ. March 2003
2. Bleiberg H: A new class of antiemetics: the NK-1 receptor antagonists. Curr Op Oncol 2000; 12:284-288.
3. Campos D, Pereira JR, Reinhardt RR et al: Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. J Clin Oncol 2001; 19:1759-1767.
4. Sorbera LA, Castaner J & Bayes M et al: Aprepitant and L-758298. Drugs Future 2002; 27(3):211-222.
5. Diemunsch P & Grelot L: Potential of substance P antagonists as antiemetics. Drugs 2000; (60):533-546.
6. DeVane CL: Substance P: a new era, a new role. Pharmacotherapy 2001; 21(9):1061-1069.
7. van Belle S, Lichninitser MR, Navari RM et al: Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists L-758,298 and MK-869. Cancer 2002; 94(11):3032-3041.
8. Anon: MK 869. Drugs 2002; 3(3):200-203.
9. Tattersall FD, Rycroft W, Cumberbatch M et al: The novel NK1 receptor antagonist MK-0869 (L-754,030) and its water soluble phosphoryl prodrug, L-758,298, inhibit acute and delayed cisplatin-induced emesis in ferrets. Neuropharmacology 2000; 39:652-663.
10. Amerisource-Bergen Online Catalog Average Wholesale Price (AWP)

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